CODEL: Phase III study of RT, RT + Temozolomide (TMZ), or TMZ for newly-diagnosed 1p/19q Codeleted Oligodendroglioma. Analysis from the initial study design

Jaeckle, Kurt A ; Ballman, Karla V ; van den Bent, Martin ; Giannini, Caterina ; Galanis, Evanthia ; Brown, Paul D ; Jenkins, Robert B ; Cairncross, J Gregory ; Wick, Wolfgang ; Weller, Michael ; Aldape, Kenneth D ; Dixon, Jesse G ; Anderson, S Keith ; Cerhan, Jane H ; Wefel, Jeffrey S ; Klein, Martin ; Grossman, Stuart A ; Schiff, David ; Raizer, Jeffrey J ; Dhermain, Frederick ; Nordstrom, Donald G ; Flynn, Patrick J ; Vogelbaum, Michael A

Abstract: BACKGROUND We report the analysis involving patients treated on the initial CODEL design. METHODS Adults (>18) with newly-diagnosed 1p/19q WHO grade III oligodendroglioma were randomized to RT (5940 cGy) alone (Arm A); RT with concomitant and adjuvant temozolomide (TMZ) (Arm B); or TMZ alone (Arm C). Primary endpoint was overall survival (OS), Arm A versus B. Secondary comparisons were performed for OS and progression-free survival (PFS), comparing pooled RT arms versus TMZ-alone arm. RESULTS Thirty-six patients were randomized equally. At median follow-up of 7.5 years, 83.3% (10/12) TMZ-alone patients progressed, versus 37.5% (9/24) on the RT arms. PFS was significantly shorter in TMZ-alone patients compared to RT-treated patients (HR=3.12; 95% CI: 1.26, 7.69; p=0.014). Death from disease progression occurred in 3/12 (25%) of TMZ-alone patients and 4/24 (16.7%) on the RT Arms. OS did not statistically differ between arms (comparison underpowered). After adjustment for IDH status (mutated/wildtype) in a Cox regression model utilizing IDH and RT treatment status as co-variables (Arm C vs pooled Arms A+B), PFS remained shorter for patients not receiving RT, (HR= 3.33; 95% CI: 1.31, 8.45; p=0.011), but not OS ((HR = 2.78; 95% CI 0.58, 13.22, p=0.20). Grade 3+ adverse events occurred in 25%, 42% and 33% of patients (Arms A, B, and C). There were no differences between Arms in neurocognitive decline comparing baseline to 3 months. CONCLUSIONS TMZ-alone patients experienced significantly shorter PFS than patients treated on the RT Arms. The ongoing CODEL trial has been redesigned to compare RT+PCV versus RT+TMZ.

DOI: https://doi.org/10.1093/neuonc/noaa168

J; Vogelbaum, Michael A (2021). CODEL: Phase III study of RT, RT + Temozolomide (TMZ), or TMZ for newly-diagnosed 1p/19q Codeleted Oligodendroglioma. Analysis from the initial study design. Neuro-Oncology, 23(3):457-467.
DOI: https://doi.org/10.1093/neuonc/noaa168

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Kurt A. Jaeckle[1], Karla V. Ballman[2], Martin van den Bent[3], Caterina Giannini[4] ,Evanthia Galanis[4], Paul D. Brown[4] , Robert B. Jenkins[4] , J Gregory Cairncross[5], Wolfgang Wick[6], Michael Weller[7], Kenneth D. Aldape[8], Jesse G. Dixon[9], S. Keith Anderson[9] , Jane H. Cerhan[10], Jeffrey S. Wefel[11] , Martin Klein[12] Stuart A. Grossman[13], David Schiff[14] , Jeffrey J. Raizer[15] , Frederick Dhermain[16] , Donald G. Nordstrom[17] , Patrick J. Flynn[18], Michael A. Vogelbaum[19]

[1] Department of Neurology, Mayo Clinic Florida, Jacksonville FL; [2]Alliance Statistics and Data Center, Weill Cornell Medicine, New York, NY; [3] Brain Tumor Center, Erasmus MC Cancer Center, Erasmus University Medical Center, Rotterdam, The Netherlands; [4] Department of Radiation Oncology, Mayo Clinic, Rochester MN; [5] Department of Clinical Neurosciences, Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, Alberta, Canada; [6] Neurologische Klinik, University of Heidelberg, Heidelberg Germany; [7] Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland; [8] Department of Neuropathology, University of Texas MD Anderson Cancer Center, Houston, TX; [9]Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; [10] Departments of Psychiatry and Psychology; [11] Departments of Neuro-Oncology and Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX; [12] Department of Medical Psychology, VU University Medical Center, Amsterdam, The Netherlands; [13] Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore MD; [14] Department of

Neurology, University of Virginia, Charlottesville, VA; [15] Department of Neurology, Northwestern University, Chicago, IL; [16] Department of Radiation Therapy, Institut de Cancerologie Gustave Roussy, Villejuif France, [17] Medical Oncology, France Abben Cancer Center, Spencer, IA; [18] Medical Oncology, Minnesota Oncology, Northfield MN; [19] Dept. of Neurosurgery, Cleveland Clinic, Cleveland OH

Corresponding Author:

Kurt A. Jaeckle, MD

Mayo Clinic Florida

4415 Mangurian, 4500 San Pablo Road, Jacksonville FL 32224

Phone: 904-953-7102

Fax: 904-953-0757

Email: jaeckle.kurt@mayo.edu

Running Title: CODEL: Phase III trial of RT vs RT/TMZ vs TMZ

Funding: The research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology), UG1CA233320, UG1CA233329, UG1CA232760; U10CA180820 (ECOG-ACRIN); U10CA180863 (CCTG); and U10CA180868 (NRG). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of Interest: The authors declare no conflicts of interest with the work described in this manuscript.

Word Count: 5932

Authorship:

Concept or Design: KAJ, KVB, MAV, CG, KDA, JHC, JSW, RBJ, JGC, SAG, EG, PDB, MW, WW, MVDB

Data Acquisition: KAJ, MAV, CG, KDA, JHC, JSW, DGN, RBJ, JJR, PJF, FD, JGC, SAG, EG, PDB, DS, MW, WW, MVDB

Data Analysis: KVB, SKA, JGD, TJZ

Data Interpretation KAJ, KVB, MAV, SKA, JGD, TJZ, MW, WW, MVDB

Draft or Revise Article: KAJ, KVB, MAV, JGD, SKA, CG, KDA, JHC, JSW, RBJ, MK, JJR, FD, JGC, SAG, EG, PDB, DS, MW, WW, MVDB

Approve Final Version: KAJ, KVB, MAV, JGD, SKA, TJZ, CG, KDA, JHC, JSW, RBJ, MK, JJR, PJF, FD, JGC, SAG, EG, PDB, DS, MW, WW, MVDB

Key Points: Patients with newly diagnosed 1p/19q codeleted anaplastic oligodendroglial tumors, treated with temozolomide alone experienced significantly shorter progression-free survival than the pooled group of patients treated with radiotherapy and radiotherapy plus temozolomide.

Key words: CODEL; 1p19q; codeleted; N0577; oligodendroglioma

Importance of the study:

The initial CODEL Phase III randomized trial for patients with newly diagnosed 1p/19q codeleted anaplastic oligodendroglial tumors gliomas compared survival outcome following radiotherapy (RT) alone (control arm) vs. RT with concurrent and adjuvant temozolomide (TMZ). A third TMZ-alone exploratory randomization arm was included as well, based on common clinical practice at the time of design. The RT-alone control arm was changed to RT + adjuvant PCV following reports from EORTC 26951 and RTOG 9402, which showed a survival benefit of added PCV for this cohort. In our analysis of the patients treated on the original CODEL design, we found that TMZ-alone treated patients experienced significantly shorter PFS than patients treated on the RT Arms. When combined with prior reported data, our results suggest that the current standard of care for these patients should include both radiation and chemotherapy.

ABSTRACT

BACKGROUND: We report the analysis involving patients treated on the initial CODEL design. METHODS: Adults (>18) with newly-diagnosed 1p/19q WHO grade III oligodendroglioma were randomized to RT (5940 cGy) alone (Arm A); RT with concomitant and adjuvant temozolomide (TMZ) (Arm B); or TMZ alone (Arm C). Primary endpoint was overall survival (OS), Arm A versus B. Secondary comparisons were performed for OS and progression-free survival (PFS), comparing pooled RT arms versus TMZ-alone arm. RESULTS: Thirty-six patients were randomized equally. At median follow-up of 7.5 years, 83.3% (10/12) TMZ-alone patients progressed, versus 37.5% (9/24) on the RT arms. PFS was significantly shorter in TMZ-alone patients compared to RT-treated patients (HR=3.12; 95% CI: 1.26, 7.69; p=0.014). Death from disease progression occurred in 3/12 (25%) of TMZ-alone patients and 4/24 (16.7%) on the RT Arms. OS did not statistically differ between arms (comparison underpowered). After adjustment for IDH status (mutated/wildtype) in a Cox regression model utilizing IDH and RT treatment status as co-variables (Arm C vs pooled Arms A+B), PFS remained shorter for patients not receiving RT, (HR= 3.33; 95% CI: 1.31, 8.45; p=0.011), but not OS ((HR = 2.78; 95% CI 0.58, 13.22, p=0.20). Grade 3+ adverse events occurred in 25%, 42% and 33% of patients (Arms A, B, and C). There were no differences between Arms in neurocognitive decline comparing baseline to 3 months. CONCLUSIONS: TMZ-alone patients experienced significantly shorter PFS than patients treated on the RT Arms. The ongoing CODEL trial has been redesigned to compare RT+PCV versus RT+TMZ.

INTRODUCTION

CODEL (NCCTG/Alliance for Clinical Trials in Oncology N0577; European Organisation for Research and Treatment Center (EORTC) 26081-22086; NRG 1071; Canadian Cancer Trials Group (CCTG) CEC.6) is an ongoing National Cancer Institute (NCI)-sponsored, international intergroup, prospective randomized phase III trial for patients with newly diagnosed 1p/19q codeleted oligodendroglial tumors. The original design included randomization of patients to radiotherapy (RT) alone (Arm A); RT plus concomitant and adjuvant temozolomide (TMZ) (Arm B); or TMZ alone (Arm C). The primary objective of the trial was to compare overall survival (OS) between patients on Arms A and B. A secondary analysis compared OS and progression-free survival (PFS) between patients treated with RT (on the pooled Arms A + B) versus Arm C patients. After active enrollment began, results from RTOG 9402 and EORTC 26951 became available, which showed a survival benefit with the addition of procarbazine, lomustine and vincristine (PCV) to RT versus RT alone.[1, 2] Accordingly, CODEL was redesigned, replacing the RT alone control arm with RT followed by adjuvant PCV, using the schedule utilized in EORTC 26951. Later, the TMZ-alone treatment arm was dropped, in part due to the findings from the current analysis. As the data from the initial patients enrolled in CODEL will not be utilized in the primary analysis for the redesigned CODEL study, the analysis is reported herein.

METHODS

Eligibility

Eligible patients included adults (age ≥ 18 years) with newly diagnosed, 1p/19q codeleted WHO grade III anaplastic oligodendroglial tumors. In the North American patients, histologic diagnosis and 1p/19q status were centrally confirmed at the Alliance/NCCTG central laboratory at Mayo Clinic (C.G., R.J.); in EORTC, pathology was centrally confirmed and 1p/19q codeletion status determined in the process of screening for EORTC 26053-22054 (CATNON). Isocitrate dehydrogenase (IDH) status was not required for eligibility, but was retrospectively obtained in 35/36 (97%) of patients, as determined by immunohistochemistry (IHC) for IDH R132H, or by sequencing. If IDH status was not known, tumor tissue banked per protocol was evaluated by IHC for IDH in the Pathology Research Core, Mayo Clinic Rochester., For those found to be IDH wild- type (WT) by IHC and with tumor tissue available, ,sequencing for IDH 1 and 2 was performed at the Clinical Genomics Laboratory, Mayo Clinic, Rochester MN.

Additional eligibility criteria included that patients: were ≤ 3 months from surgical diagnosis and recovered from effects of surgery; had acceptable hematologic parameters (absolute neutrophil count (ANC) ≥ 1500 / uL; platelet count ≥ 100,000 / uL; hemoglobin ≥ 9 gm/dL, serum total bilirubin ≤ 3 times upper limit of normal (ULN), aspartate aminotransferase (AST) ≤ 3 times ULN, and creatinine ≤ 1.5 ULN); had Eastern Cooperative Oncology Group (ECOG) performance status 0-2; were willing to provide tissue samples for translational research studies; were able to complete neurocognitive testing and quality of life questionnaire without assistance; and were able to provide informed, written consent. Women of child-bearing potential had a negative pregnancy test, and expressed willingness to use contraception. Patients were ineligible if they had comorbid medical conditions compromising safety on this treatment; were immunocompromised (other than receiving steroids); had active serious infection or history

of HIV infection; had recent (< 6 months) history of myocardial infarction or congestive heart failure; had another active malignancy, with the exception of non-melanomatous skin or cervical cancer; or were receiving other active therapies directed at the central nervous system neoplasm.

Study participants were required to sign Institutional Review Board-approved, protocol-specific informed consent documents in accordance with federal, and institutional guidelines. Site participation required protocol approval by local institutional review boards, in accordance with assurances filed with the U.S. Department of Health and Human Services, or as required by the applicable national legislation of non-US countries. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The trial is registered in the public domain (clinicaltrials.gov; NCT00887146).

Study Design and Treatment

Patients were randomized to Arm A, RT (5940 cGy in 33 fractions) alone; Arm B, RT + concomitant TMZ (75mg / m2 /day) followed by adjuvant TMZ (150-200 mg / m2, days 1-5 every 28 days) for up to 12 cycles; or Arm C, TMZ alone (150-200 mg / m2, days 1-5 every 28 days for up to 12 cycles (**Figure 1**). The decision to extend TMZ treatment beyond 6 cycles, for up to 12 cycles, was left to the treating investigator, without protocol-defined progression or development of adverse events meeting criteria for discontinuation of therapy. Patients were randomized in a 1:1:1 fashion with the following stratification factors: age ($\geq$ 50 versus $\leq$ 50 years), registering group (NCI/CCTG versus EORTC), and ECOG performance status (0-1 versus 2). Temozolomide was provided initially by Schering-Plough, and later Merck

Pharmaceuticals, Kenilworth, NJ. Prophylaxis for *Pneumocystis jirovecii* was required in patients receiving temozolomide.

For North American sites, the radiation treatment volume was defined as the T2 hyperintensity on FLAIR (fluid-attenuated inversion recovery) or T2-weighted MR images including the surgical cavity, with a 1.0 cm margin anatomically constrained, plus a 5 mm planning target volume (PTV) margin to account for daily setup variation. This volume received 5040 cGy in 28 daily fractions if a sequential boost technique was used or 5445 cGy in 33 daily fractions if a concomitant boost technique was utilized. If enhancing tumor was present, this represented the boost volume with the resection cavity, plus a 5-mm PTV margin. If no tumor enhancement, the boost was defined as the original volume, but with no extra margin, except for the 5-mm PTV margin. For sequential boost technique, 900 cGy was administered in 5 daily fractions (total dose 5940 cGy in 33 daily fractions). For concomitant boost technique, the total dose to the boost volume was 5940 cGy in 33 daily fractions. EORTC sites utilized a single Gross Tumor Volume target (with no boost), defined as the entire region of T2 hyperintensity plus the region of enhancement on either the post- operative MRI (if available), or on the preoperative scan.

Endpoints

In the initial CODEL study, the primary endpoint was the comparison of OS between Arm A versus Arm B. OS was measured from the time of randomization until death. Secondary endpoints included comparison of PFS (Arm A vs B) and time to neurocognitive progression

(Arm C vs Arm B). However, this initial study was temporarily closed prematurely at the request of the Alliance Data Safety Monitoring Committee, in part due to the data observations regarding Arm C patients, and due to reports from the late analyses of RTOG 9402 and EORTC 26951 which impacted the control arm of this initial CODEL study. Adequate events were not observed for the protocol-defined primary and secondary endpoint comparisons. Thus, we performed an initially unplanned secondary analysis to compare PFS of patients randomized to Arm C to the pooled Arm A and B patients. PFS was measured as the time from randomization until investigator-defined progression (earliest of either clinical progression or radiographic progression, protocol-defined per NCCTG criteria[3] (see Supplemental Material), or death without documented progression. Patients alive at the time of analysis (5/4/2020) were censored at their last follow- up date. Patients having biopsy or subtotal resection were evaluated for clinical and radiographic response utilizing NCCTG criteria and designated as either complete response, partial response (PR), or regression (REGR) sustained at least 4 weeks; or as progression (PROG), as compared with the pre-treatment baseline assessment.

Neurocognitive timepoints varied slightly by arm, and compliance with the schedule was limited. Thus, the only meaningful analysis that could be conducted compared baseline assessments with those competed within the first 3 months of treatment. A Reliable Change Index (RCI), representing the 90% confidence interval for test-retest variability (RCI90) was utilized to compare baseline and 3 month subtests. Cognitive decline was defined as a worsening from baseline greater than the respective RCI90 normative values on any one of the following subtests: Hopkins Verbal Learning Test-Revised (HVLT-R) [4]; Total Recall, Delayed Recall, and Delayed Recognition; Controlled Oral Word Association (COWA) [5]; or Trail Making Test Part A

and B[6]. Credentialing of site personnel was required for administration of cognitive testing (J.C., J.W or M.K). Quality of life (QoL) was assessed via two instruments: the EORTC quality of life questionnaire core-30 (QLQ-C30, version 3) and EORTC quality of life questionnaire-brain cancer module (QLQ-BN20). The protocol defined schedule for cognitive testing and QoL reporting was baseline, 4-6 weeks post RT (Arms A and B), or at the beginning of every other treatment cycle (Arm C), then 8 weeks for 18 months, then every 12 weeks until progression.

Adverse events were evaluated with the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Arms A and B assessments (neurological exam, neuroimaging, and blood profiles) were performed at baseline, 4-6 weeks post RT, and at the beginning of every other treatment cycle (Arm C), then every 8 weeks for 18 months, and then every 12 weeks until progression. Patients who progressed were followed clinically until death. Per protocol, MRI scans were required unless contraindicated (e.g., presence of pacemaker), in which case CT scans were allowed; however in review, all patients were followed by MRI. Sites were required in advance to meet credentialing standards for RT.

Statistical considerations

The study was powered to detect OS hazard ratio (HR) of 0.67 or less when comparing Arm B to Arm A. A sample size of 219 patients per arm would have 80% power with a one-sided alpha = 0.05 using a log rank test, [7] assuming the median survival for the control arm (Arm A) was 7.2 years. The final OS analysis was to be performed when 178 deaths were observed. The sample size for the secondary analysis, comparing PFS between Arm C and Arms A and B,

was to include 50 patients in Arm C and 100 patients in Arms A and B , performed when 75 progression events were observed. All analyses were based on the intention-to-treat principle, with all eligible patients belonging to the treatment arm to which they were randomized. The distributions of OS and PFS were estimated using the Kaplan-Meier method [8] along with median survival, and corresponding 95% confidence intervals (CI). The differences between Kaplan-Meier survival curves were evaluated with a log rank test. Cox models were used to generate point estimates and hazard ratios (HRs) for comparisons between arms, comparisons between IDH mutation status, and for comparisons between arms while adjusting for IDH mutation status. Differences in the proportions of patients with grade 3+ adverse events among/between treatment arms were evaluated with a chi-square test. Neurocognitive analysis across the three arms was based on the change from baseline to the 3-months evaluation. Differences in proportions of patients with cognitive decline among/between treatment were evaluated with a chi-square test. QoL analysis across all three arms was based on the change from baseline to the 3-month QLQ-C30 and QLQ-BN20 evaluations. Change-from-baseline values were compared across the arms using the Kruskal-Wallis test. All analyses were completed with SAS version 9.4M5.
Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Data quality was ensured by review of data by the Alliance Statistics and Data Center and by the study chairperson following Alliance policies. The study was monitored by the Alliance Data and Safety Monitoring Board.

RESULTS

Thirty-six patients with 1p/19q codeleted anaplastic (WHO Grade III) glioma were randomized between November, 2009 and December, 2011 (Arm A-12; Arm B-12; Arm C-12) and included in this analysis. The North American NCI-Sponsored Cooperative Groups accrued 19 patients (53%) and EORTC accrued 17 patients (47%).The treatment arms were balanced for age, ECOG status, and extent of resection (**TABLE 1**).

Patient outcomes

There were 8 deaths: 3 on Arm A, 1 on Arm B, and 4 on Arm C. The median follow-up was 7.5 years. Overall survival time (**FIGURE 2**) was not statistically different between RT alone (Arm A) and RT+TMZ (Arm B) with median OS was not reached in either arm (Figure 2A); (HR 2.74 (95% CI: 0.28 to 26.43 log rank p-value = 0.36); however, this comparison is significantly underpowered. OS difference also failed to reach statistical significance with regard to patients treated on Arm C, compared to the patients on Arms A and B combined (log rank p-value = 0.27, Figure 2B). The median OS was not reached in either group, with observed HR 2.14 (95% CI: 0.53 to 8.61). The 3- and 5-year OS rates were 75% and 67%, respectively, for TMZ-alone Arm C patients compared to 96% and 91% for patients treated with RT (Arms A andB). When comparing patients treated without TMZ (Arm A) versus those treated with TMZ (pooled Arms B+C), there were no significant differences in PFS (median = 4.2 yrs. vs. 6.5 yrs., respectively; HR=1.44, 95% CI: 0.58 to 3.60; log rank p=0.43) or OS (neither reached median; HR=1.12, 95% CI: 0.27 to 4.71; log rank p=0.87).

With a median clinical follow-up of 6.6 years, there were 19 disease progression events; 10 on Arm C1 on Arm B, and 8 on Arm A. Radiographic progression was listed in the case report forms as the justification for determination of progression in 18 patients, with the remaining patient listed as 'local brain failure and clinical progression'. Median progression-free survival (**FIGURE 3**) was significantly shorter in TMZ alone-treated patients compared with those treated with RT (Arm A+B) (2.9 yrs. vs. not reached, respectively; HR=3.12, 95% CI: 1.26 to 7.69; log rank p=0.009). The 3- and 5-year PFS rates were 50% and 33% in the TMZ alone-treated patients, respectively, compared to 83% and 56% in those treated with RT (Arms A+B). There were six response-evaluable patients on each arm. No statistical difference (p=0.52) was observed across arms for patients with a tumor response (REGR, partial response (PR), or complete response (CR) lasting at least 4-weeks: there were no responses on Arm A (0%), 2 responses on Arm B (33%), and 1 response on Arm C (17%).

All of the Arm C patients who progressed on TMZ alone subsequently received RT or RT+TMZ, and 3 also underwent re-resection, all with pathologic confirmation of tumor progression. One progressing patient each on Arm A and Arm B underwent subsequent re-resection, both with pathologic confirmation of tumor progression.

IDH Status

Tissues from 35 of the 36 (97%) patients (Arm A - 12; Arm B - 11; Arm C - 12) were available for IDH analysis. Of these, 30 (86%) were IDH mutated (Arm A - 11; Arm B - 10; Arm C - 9) and 5 were IDH wild type (WT) (Arm A - 1; Arm B - 1; Arm C - 3). IDH 1 and 2

WT status was confirmed by sequencing of available tumor tissue from 2/5 of these patients; for the purposes of this analysis, the 3 remaining patients were considered IDH WT based on IHC results alone, When comparing the IDH mutated and non-mutated patients, PFS differed, but did not reach statistical significance (median, 5.4 yrs. vs. 0.8 yrs., respectively; HR=0.35, 95% CI: 0.12 to 1.06; log rank p = 0.052), but OS differed significantly (median = not reached vs. 2.0 yrs., respectively; HR=0.07, 95% CI: 0.01 to 0.31; log rank p < 0.01). Cox regression was used to adjust for IDH mutation status. The model included IDH mutational status and RT treatment status as co-variables (Arm C vs pooled Arms A+B), as no significant interaction between these two variables was observed (OS, p=0.995; PFS, p=0.068). Again, PFS was shorter for patients who did not receive RT, (HR= 3.33; 95% CI: 1.31, 8.45; p=0.011). In the analysis of OS, RT treatment status (Arm C vs A+B) was not statistically associated with OS (HR = 2.78; 95% CI 0.58, 13.22; p=0.200).

Adverse Events

No statistical difference was observed across treatment arms with respect to the proportion of patients with at least one Grade 3 or 4 adverse event (25%, 42%, and 33% on Arms A, B and C, respectively; p = 0.69). There was one patient in each arm that experienced a grade 4 event and no grade 5 adverse events were observed. There were 2 patients on Arm A, 4 patients on Arm B, and 3 patients on Arm C that experienced grade 3 adverse events. Two RT-treated patients withdrew from treatment due to adverse events, one Arm A patient with empyema requiring surgery, and one Arm B with neutropenia. No Arm C patients withdrew from treatment due to adverse events.

Cognitive decline

Twenty-nine (81%) patients completed the full cognitive test battery assessments for the baseline and 3-month time points (**TABLE 2B**). Overall, there was deterioration in at least one test results by > RCI90 at 3 months compared with baseline pre-treatment testing in 21 patients (72%). Of the patients demonstrating cognitive decline at 3 months, none met protocol-defined criteria for clinical progression. There was no significant difference in proportions of patients who declined (Arm C, 67%; Arms A and B, 75% p=0.99). Comparisons of individual subtests also did not yield statistically significant differences between Arm C versus Arms A and B.

Quality of Life (QoL)

QoL assessments for change from baseline to timepoint-1 (3 mos.) were available for 21 patients in pooled Arms A and B, and 9 in Arm C. Changes from baseline to timepoint-2 were available from 14 and 6 patients in arms A+B and Arm C, respectively. There was no statistical difference between Arm A+B and Arm C as measured by the QLQ-C30 overall QoL. Slight increases from baseline were noted in the averages for both groups of patients at both timepoint-1 (Arms A+B: 5.6 points, Arm C: 4.6 points; p=0.89) and timepoint-2 (Arms A+ B: 7.1 points, Arm C: 4.2 points; p=0.67). Two subscales showed statistically significant differences between Arms A+B versus Arm C for at least one time point: the QLQ-C30 subscale for constipation showed an average improvement at timepoint-1 for Arm C and no change in Arms A+ patients (18.5 points versus 0.0 points; p=0.002). The QLQ-BN20 subscale for Motor Dysfunction

showed an average improvement at timepoint-2 for Arm C and a decline for patients in Arm A+B combined (7.4 points versus -4.0 points; p=0.018).

DISCUSSION

From 1985 to 2000, many physicians recommended treatment of 1p/19q codeleted patients with RT alone, or RT + PCV. In the 2000s, there was a shift to recommendation of either chemotherapy (PCV or TMZ), or RT + TMZ, [9] which occurred in the absence of comparative data from randomized prospective trials. As of this writing, TMZ has not yet been approved by the U.S. Food and Drug Administration for the specific indication of newly diagnosed WHO grade II or III oligodendroglioma.

The original CODEL study was designed with an RT-alone control arm, as at the time there were no conclusive data demonstrating OS benefit with the addition of PCV chemotherapy to RT, compared with RT alone. At the time (2006), the initial analyses from the RTOG 9402 and EORTC 26951 did not demonstrate superiority of RT+ PCV (neoadjuvant or adjuvant) over RT alone. [10,11] Accordingly, the main objective of the original CODEL study was to determine whether the addition of TMZ to RT might result in superior survival compared with RT alone, when (at the time) the addition of PCV to RT had not.

The original CODEL design became obsolete after mature analyses from RTOG 9402 and EORTC 26951 showed inferior survival with RT alone as compared with RT+PCV. [1, 2] Both randomized trials suggested that 1p/19q codeletion predicted benefit to addition of

chemotherapy, More recent reports suggest that O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter hypermethylation and IDH mutation may be superior predictive factors. [12, 13] The current WHO 2016 classification requires that both 1p/19q codeletion and IDH mutation be present for a diagnosis of oligodendroglioma. [14]

The authors acknowledge the limitations of this study. The current analysis involved a small sample size and comparisons are likely underpowered. It is noted that central confirmation of radiographic progression was not performed, although the specific reasons for determination of progression was reviewed as documented in the protocol case report forms for each patient. We cannot completely exclude introduction of bias regarding timing of progression, however, this is felt unlikely. In review of the case report forms, radiographic progression was listed as the determining cause for all progressing patients except the latter progressing due to 'local brain failure and clinical progression'. Furthermore, the definition of progression was clearly protocol-specified, the NCI Cooperative Group, CCTG and EORTC site investigators are experienced in clinical trial conduct, and several different centers accrued patients to the different treatment arms.

With these caveats in mind, our data showed that treatment with TMZ alone was associated with earlier time to tumor progression and significantly shorter PFS compared with those treated with radiotherapy (RT and RT + TMZ). Although the observed median PFS of 2.9 years for newly-diagnosed codeleted patients treated with TMZ alone appears shorter than expected, it is similar to that previously reported in retrospective or prospective studies involving 1p/19q codeleted patients treated with TMZ alone (**TABLE 3)**, [15-19] Given our data and prior

reports indicating median PFS of 8.4-12.8 years with RT + PCV. [1,2,] the Alliance Data Monitoring Committee and NCI recommended closure of the TMZ alone Arm in CODEL as it was felt that it would be unlikely that patients treated with TMZ alone would experience superior survival than those treated on the RT arms. Although OS was longer on the RT-containing arms it did not achieve statistical significance, but this comparison was underpowered. It is also possible that OS curves converged in part due to subsequent treatment, given that all patients treated with TMZ alone received RT-containing regimens at relapse. Based on these data and prior Phase III results, the ongoing CODEL trial has been re-designed as a two-arm comparison of RT followed by adjuvant PCV (control, based on RTOG 9402 and EORTC26951) versus RT with concomitant and adjuvant TMZ, with PFS as the primary endpoint.

We did not find significant differences in cognitive function between treatment arms at 3 months, but the number of patients tested was small and hence comparisons are underpowered. The lack of later assessment points precludes meaningful conclusions. Comprehensive mandatory serial cognitive and QoL assessments are required in the ongoing CODEL study, which we hope will clarify the comparative toxicities of RT+ PCV versus RT+TMZ. The comparative toxicities of PCV chemotherapy alone versus RT + PCV may also be clarified in the ongoing POLCA study (NCT02444000).

In the original CODEL design, IDH status was not required for eligibility. We were able to retrospectively identify IDH status retrospectively in 35/36 (97%) patients; 30 (86%) were IDH mutated (Arm A - 11; Arm B - 10; Arm C - 9) and 5 were IDH wild type (WT) (Arm A - 1; Arm B - 1; Arm C - 3). One might expect that IDH WT 1p/19q codeleted patients would show

earlier progression than IDH mutated patients, but when adjusting for IDH mutation status (WT vs. mut), treatment with RT (Arms A and B vs. C) remained significantly associated with longer PFS (HR= 3.33; 95% CI: 1.31, 8.45; p=0.011), and no significant interaction was observed between IDH mutation status and treatment with RT (p=0.068). One potential reason for this apparent discordance may be that only 2 of our 5 patients had confirmation of IDH WT status, as determined initially by IHC, with subsequent sequencing. It has been reported that almost all 1p/19q codeleted oligodendroglial tumors show IDH 1 or 2 mutations by sequencing, and thus it is theoretically possible that IDH WT, as determined by IHC, represented false negatives in our 3 patients. Nevertheless, we did observe significant differences in OS of codeleted patients as a function of IDH status. Given the 2016 WHO definition of oligodendroglioma now requires both 1p/19q codeletion and IDH mutation for diagnosis,[14] it is reasonable to consider the rare, 1p/19q codeleted, IDH WT patients as a separate cohort for future trials. In accord with the 2016 WHO definition, both 1p/19q codeletion and IDH mutation are now required as eligibility criteria in the ongoing CODEL study.

It is acknowledged that certain patients with 1p/19q co-deleted, IDH mutated tumors even when treated with TMZ alone, can exhibit indolent disease. [12, 21-22] It has been postulated that such variation in biological behavior may in part be explained by additional genomic alterations within 1p/19q codeleted tumors. The presence of 9p21, loss.14q loss, or *MYC* activation has been associated with unfavorable outcome in patients with 1p/19q codeleted tumors. [21] Conversely, overexpression of neuronal intermediate progenitor proteins has been associated with more indolent behavior. [22] It is expected that the comprehensive correlative multi-omics analyses which are part of the ongoing CODEL study might identify new

biomarkers that delineate prognostic subgroups, and identify important new potential therapeutic targets for future clinical trials involving this patient population.

CONCLUSIONS

We found that treatment of newly diagnosed patients with 1p/19q codeleted WHO Grade III oligodendroglial tumors with TMZ alone was associated with significantly inferior PFS as compared with patients treated with RT. When combined with prior reported data, [1, 2] our results support the assertion that the current standard of care treatment for newly diagnosed patients with 1p/19q codeleted anaplastic gliomas should include both radiation and chemotherapy. The ongoing CODEL trial should establish the comparative efficacy and toxicity of RT plus adjuvant PCV versus RT plus concomitant and adjuvant TMZ, and the integrated correlative molecular analyses may identify prognostic subgroups and new therapeutic targets for this population.

ClinicalTrials.gov Identifier: NCT00887146

Acknowledgements:

We are grateful to MSD/Merck & Co for provision of temozolomide. We acknowledge Lacombe Denis (EORTC Clinical Research Physician), Thierry Gorlia (EORTC Study Statistician), and Allgeier Anouk (EORTC Project Manager) for their contributions to the study design, protocol development and study activation within Europe; and Tyler J. Zemla for his contributions to the biostatistical analyses.

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FIGURE LEGENDS

FIGURE 1. CONSORT DIAGRAM

FIGURE 2A. OVERALL SURVIVAL (ARM A vs. ARM B)

FIGURE 2B. OVERALL SURVIVAL (ARMS A+B vs. ARM C)

FIGURE 3. PROGRESSION_FREE SURVIVAL (ARMS A+B vs. ARM C)

NCCTG ASSESSMENT CRITERIA FOR RESPONSE AND PROGRESSION

Assessment of response was based upon a) changes on enhanced MRI (or CT) scans, obtained at the protocol-defined timepoints and compared with baseline on-study scans, and b) clinical status, based on neurologic examination, performed at protocol-defined timepoints and compared with baseline examination. Patients whose postoperative scans revealed no residual tumor were classified as NED (no evidence of disease). To be evaluable for objective response (CR, PR or STAB), patients must have had response of measurable or evaluable disease on MRI (or CT) scan while remaining neurologically stable or improved, on stable or decreased doses of corticosteroids.

For the purposes of this study, response or progression status at the timing of assessment was as compared with status at baseline. Time to progression was defined as the time from randomization to time of progression.

COMPLETE RESPONSE (CR): disappearance of all visible tumor.

PARTIAL RESPONSE (PR): ≥50% reduction in the product of perpendicular diameters of the clearly demarcated contrast-enhancing mass.

REGRESSION (REGR): (Only for tumors not bi-dimensionally measurable, but clearly evaluable for response): unequivocal reduction in the size of contrast enhancement, or decrease

in mass effect, as agreed upon independently by the primary physician and the quality control physician.

STABLE DISEASE (STAB): <50% reduction to < 25% increase in the product of perpendicular diameters of the clearly demarcated contrast-enhancing mass

PROGRESSION: 25% or greater increase in the product of perpendicular diameters of the clearly demarcated contrast enhancing mass, unequivocal progression of non-measurable disease, or new lesions consistent with tumor.

TABLE 1.
PATIENT DEMOGRAPHICS

	Arm A: RT Alone (N=12)	Arm B: RT + Con TMZ (N=12)	Arm C: TMZ Alone (N=12)
Group, n (%)			
EORTC	6 (50.0%)	5 (41.7%)	6 (50.0%)
North America	6 (50.0%)	7 (58.3%)	6 (50.0%)
Age (years)			
N	12	12	12
Mean (SD)	48.3 (10.28)	48.3 (9.19)	42.5 (12.97)
Median	50.0	48.5	43.5
Range	29.0, 66.0	31.0, 64.0	18.0, 61.0
Gender, n (%)			
Female	3 (25.0%)	6 (50.0%)	2 (16.7%)
Male	9 (75.0%)	6 (50.0%)	10 (83.3%)
ECOG Performance Score, n (%)			
0	9 (75.0%)	8 (66.7%)	9 (75.0%)
1	3 (25.0%)	4 (33.3%)	3 (25.0%)
Previous Cancer, n (%)			
Yes	1 (8.3%)	0 (0.0%)	0 (0.0%)
No	11 (91.7%)	12 (100.0%)	12 (100.0%)
Side Primary Tumor, n (%)			
Right	6 (50.0%)	8 (66.7%)	9 (75.0%)
Left	5 (41.7%)	3 (25.0%)	3 (25.0%)
Bilateral	1 (8.3%)	1 (8.3%)	0 (0.0%)
Corticosteroid Therapy at Entry, n (%)			
Yes	3 (25.0%)	1 (8.3%)	4 (33.3%)
No	9 (75.0%)	11 (91.7%)	8 (66.7%)
Extent Surgical Resection, n (%)			
Biopsy	0 (0.0%)	1 (8.3%)	2 (16.7%)
Subtotal Resection	6 (50.0%)	6 (50.0%)	4 (33.3%)
Gross Total Resection	6 (50.0%)	5 (41.7%)	6 (50.0%)
Prior History Brain Tumor, n (%)			
Yes	1 (8.3%)	0 (0.0%)	1 (8.3%)
No	11 (91.7%)	12 (100.0%)	11 (91.7%)

TABLE 2.

COGNITIVE PROGRESSION AT 3 MONTHS

	Arm A: RT Alone (N=9)	Arm B: RT + Con TMZ (N=11)	Arm C: TMZ Alone (N=9)	Total (N=29)	P-value
Median Days to Testing, (range)	87 (84-105)	85 (73-130)	82 (59-97)	86 (59-130)	0.13[2]
Frequency of Deterioration[a]					
HVLT-R Immediate Recall, n (%)	1 (11.1%)	1 (9.1%)	1 (11.1%)	3 (10.3%)	0.93[1]
COWAT, n (%)	0 (0.0%)	1 (9.1%)	1 (11.1%)	2 (6.9%)	0.20[1]
Trail Making A, n (%)	1 (12.5%)	0 (0.0%)	3 (37.5%)	4 (15.4%)	0.18[1]
Trail Making B, n (%)	5 (71.4%)	3 (33.3%)	3 (42.9%)	11 (47.8%)	0.29[1]
HVLT-R Delayed Recall, n (%)	3 (33.3%)	1 (9.1%)	0 (0.0%)	4 (14.3%)	0.18[1]
HVLT-R Delayed Recognition, n (%)	2 (22.2%)	2 (18.2%)	1 (12.5%)	5 (17.9%)	0.24[1]
Progression Determination					
Neurocognitive Progression[b], n (%)	7 (77.8%)	8 (72.7%)	6 (66.7%)	21 (72.4%)	0.87[1]
Clinical Progression[c], n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA

[a] > RCI90 value decrease from baseline

[b] Number deteriorating on any one subtest > RCI90 value decrease from baseline

[c] Defined by clinical exam and/ or radiographic progression at 3 months after registration

[1] Chi-Square

[2] Kruskal-Wallis

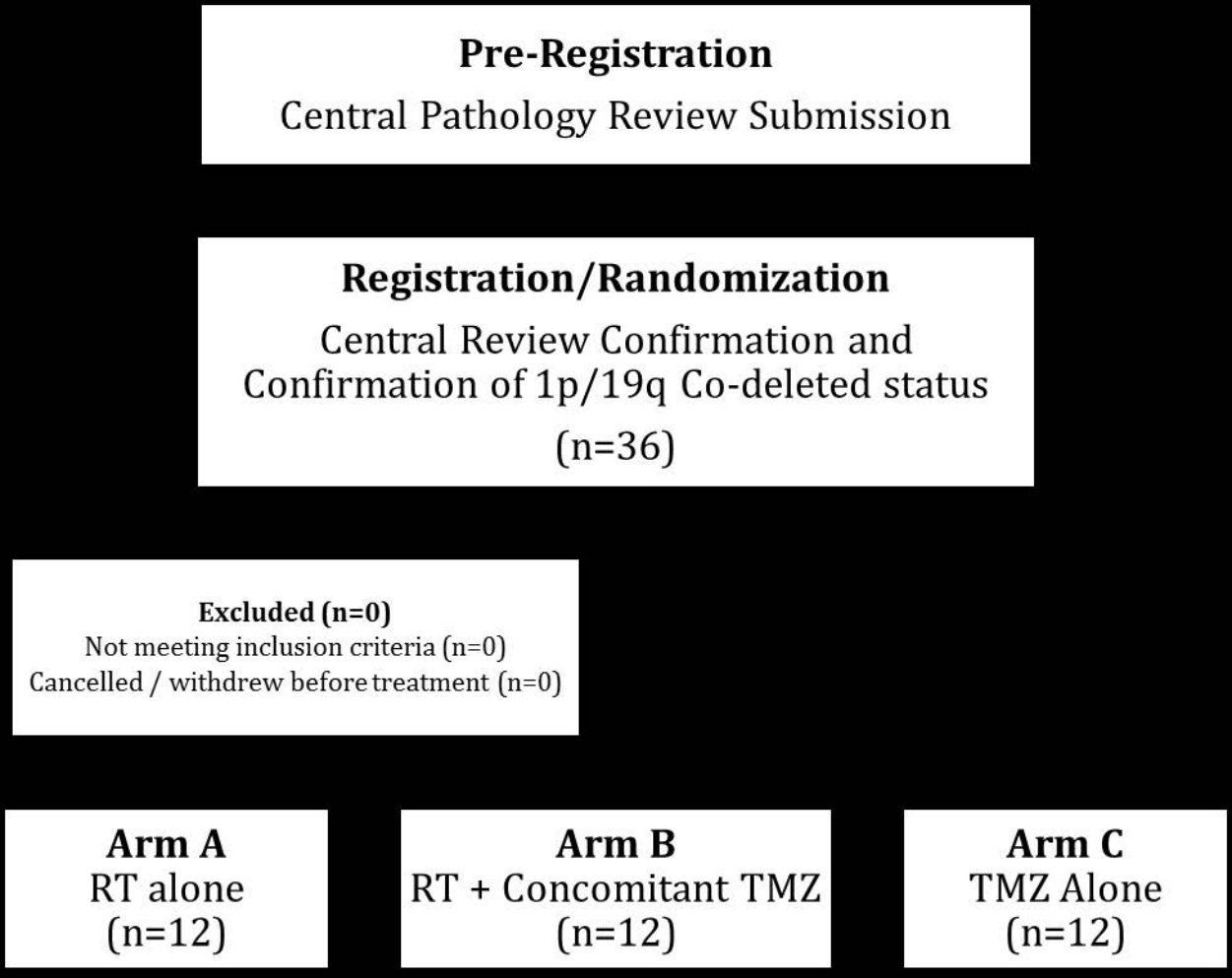
RCI=Reliable Change Index; HVLT-R=Hopkins Verbal Learning Test-Revised; COWAT=Controlled Oral Word Association Test; RT=radiotherapy; TMZ=temozolomide

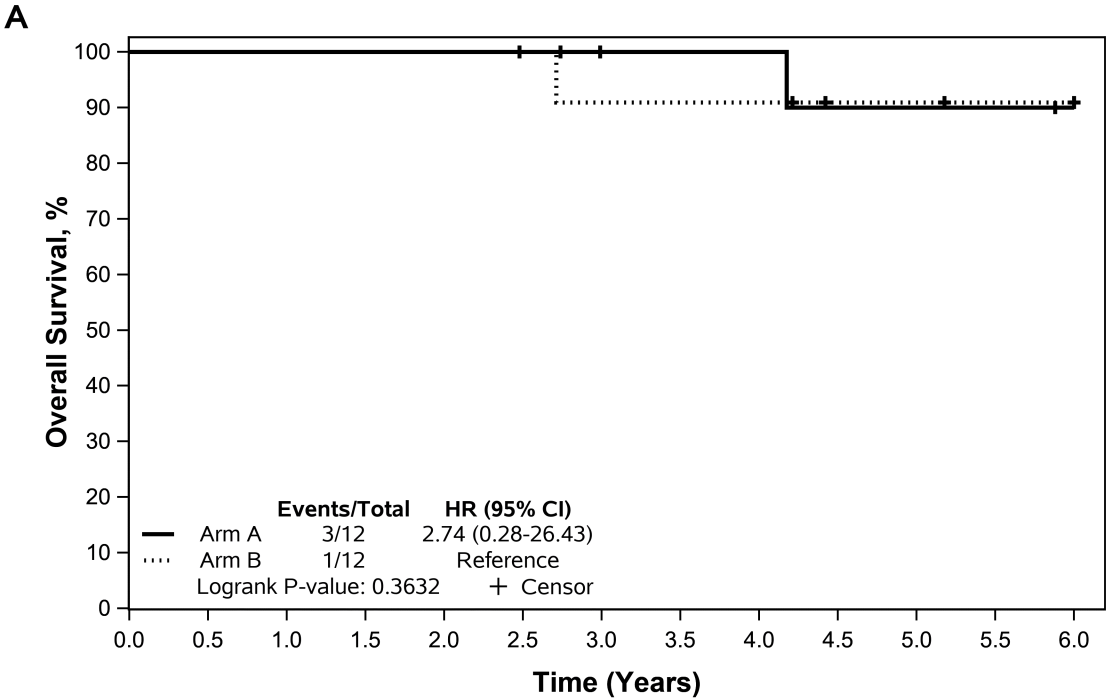
TABLE 3.

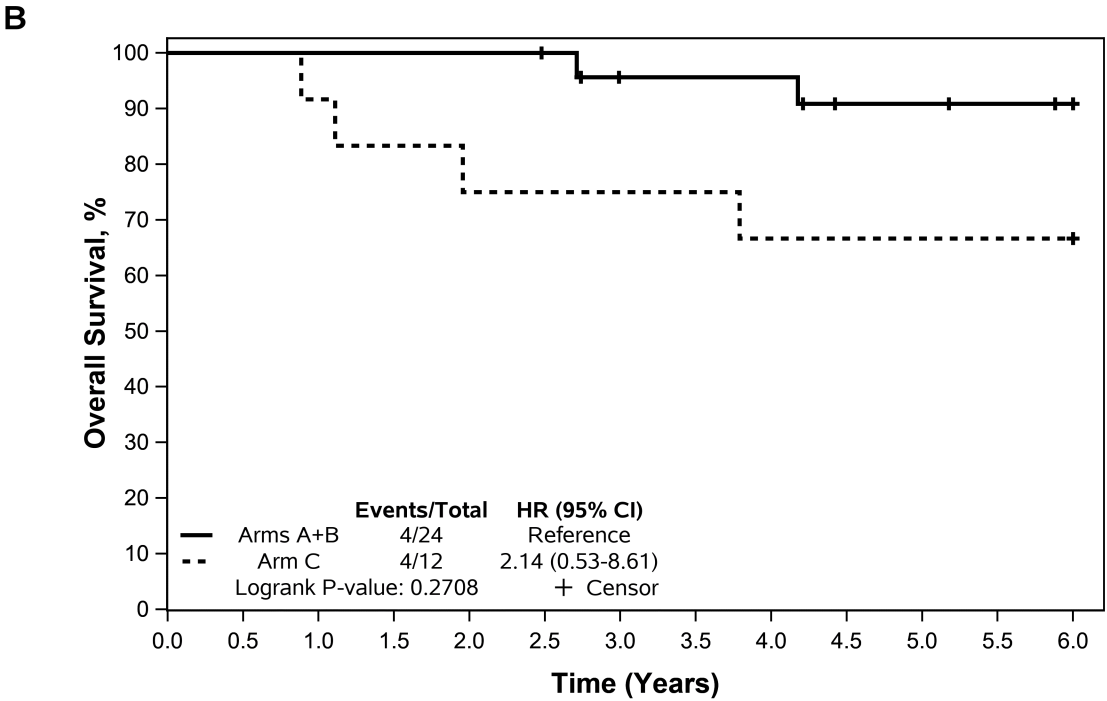
PROGRESSION OUTCOME FOLLOWING INITIAL CHEMOTHERAPY ALONE: PATIENTS WITH NEWLY DIAGNOSED, 1p/19q CODELETED ANAPLASTIC OLIGODENDROGLIOMAS

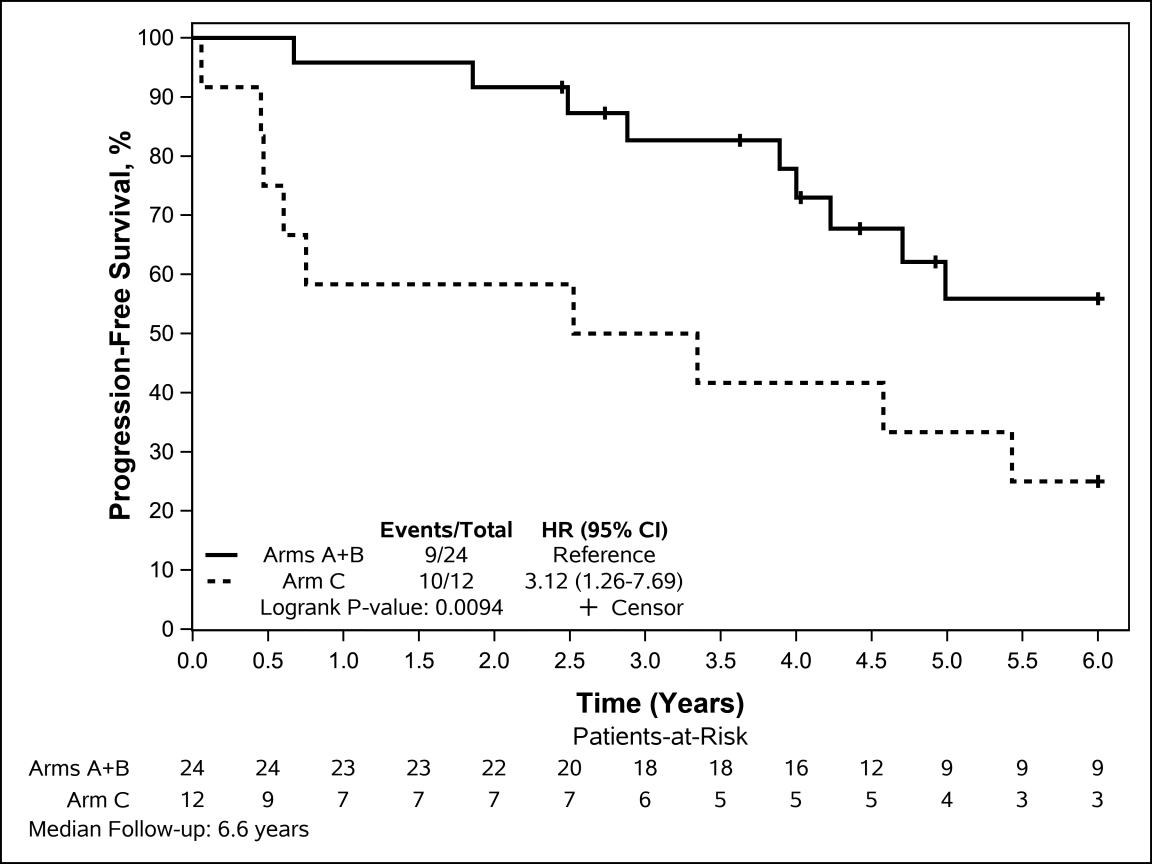
Authors	Study Type	N	Initial Treatment	Med PFS or Med TTP, (yrs)
Lassman, et al[15]	Case Series	124	TMZ PCV	3.3 7.6
Mikkelsen, et al[16]	Case Series	36	TMZ	2.4
Thomas, et al[18]	Phase II	33	TMZ → ASCT[b]	5
Wick, et al[19,a]	Phase III	17 16	TMZ PCV	4.5 9.4

[a] 1p/19q codeleted, CIMP + patients
[b] Responders to TMZ subsequently received ASCT
AO=anaplastic oligodendroglioma; AOA=anaplastic oligoastrocytoma; Med=Median; TMZ=temozolomide; PCV=procarbazine, lomustine and vincristine; HDC-ASCT=high dose chemotherapy with autologous stem cell transplant


Pre-Registration
Central Pathology Review Submission
Registration/Randomization
Central Review Confirmation and
Confirmation of 1p/19q Co-deleted status
(n=36)
Excluded (n=0)
Not meeting inclusion criteria (n=0)
Cancelled / withdrew before treatment (n=0)
Arm A
RT alone
(n=12)
Arm B
RT + Concomitant TMZ
(n=12)
Arm C
TMZ Alone
(n=12)


A
Overall Survival, %
100
90
80
70
60
50
40
30
20
10
0
Events/Total
HR (95% CI)
Arm A 3/12 2.74 (0.28-26.43)
Arm B 1/12 Reference
Logrank P-value: 0.3632
+ Censor
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Time (Years)
Patients-at-Risk
Arm A 12 12 12 12 12 12 10 10 10 9 9 9 8
Arm B 12 12 12 12 12 11 10 10 10 8 8 7 7
Median Follow-up: 6.9 years


B
Overall Survival, %
100
90
80
70
60
50
40
30
20
10
0
Events/Total
HR (95% CI)
Arms A+B 4/24 Reference
Arm C 4/12 2.14 (0.53-8.61)
Logrank P-value: 0.2708
+ Censor
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Time (Years)
Patients-at-Risk
Arms A+B 24 24 24 24 24 23 20 20 20 17 17 16 15
Arm C 12 12 11 10 9 9 9 9 8 8 8 8 8
Median Follow-up: 7.5 years


Progression-Free Survival, %
100
90
80
70
60
50
40
30
20
10
0
Events/Total
HR (95% CI)
Arms A+B 9/24 Reference
Arm C 10/12 3.12 (1.26-7.69)
Logrank P-value: 0.0094
+ Censor
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0
Time (Years)
Patients-at-Risk
Arms A+B 24 24 23 23 22 20 18 18 16 12 9 9 9
Arm C 12 9 7 7 7 7 6 5 5 5 4 3 3
Median Follow-up: 6.6 years